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EIJI SHIOJIRI, ET AL :EXAMINER: KAM, C.M.

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FOR: MELANOCYTE-STIMULATING HORMONE INHIBITORS

CERTIFICATE OF TRANSLATION

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Sir: Masao SHIMOKOSHI, a translator, residing at 356-46, Obayashi, Koshigaya-shi, Saitama-ken, Japan hereby states:

(1) that I am fluent in both the Japanese and English languages;

(2) that I translated the attached document identified as corresponding to Japanese Patent Application No. JP1999-118633 filed in Japan on April 26, 1999 from Japanese to English;

(3) that the attached English translation is a true and correct translation of Japanese Patent Application No. JP1999-118633, to the best of my knowledge and belief; and

(4) that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 USC 1001, and that such false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: November 3, 2006 By: Masao Shimokoshi

Masao SHIMOKOSHI

JP1999-118633

PATENT OFFICE
JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

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Application Number: JP1999-118633

Applicant(s): AJINOMOTO CO., INC.

Takahiko KONDO, Commissioner, Patent Office

Certification No.:

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[Attachment Name] Specification 1

[Attachment Name] Abstract 1

[General Authorization] 9607453

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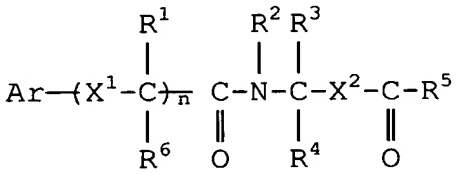
[Document Name] SPECIFICATION

[Title of the Invention] Melanocyte-Stimulating Hormone Inhibitors

[Scope of Claim for Patent]

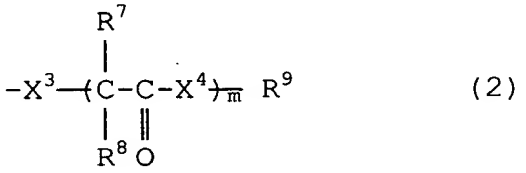
[Claim 1] Di- or tripeptide derivatives having a naphthyl group and represented by the following general Formula (1) or salts thereof:



(1)

wherein Ar represents a naphthyl group which may have substituent(s), R^1, R^2 and R^3 represent each independently a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms which may have substituent(s), R^4 represents a hydrogen atom, an amino acid side chain, an amino group, an amidino group, a guanidinyl group, a straight-chain or branched-chain aminoalkyl group having 1 to 6 carbon atoms, a straight-chain or branched-chain amidinoalkyl group having 1 to 6 carbon atoms, a straight-chain or branched-chain guanidinoalkyl group having 1 to 6 carbon atoms, or an amidinoaryl group having 6 to 12 carbon atoms, all of which group may have substituent(s), X^1 is actually absent (i.e., nothing) or an alkylene group having 1 or 6 carbon atoms, an aminoalkylene group having 1 to 6 carbon atoms which may have as a substituent a straight-chain or branched-chain alkyl group having 0 to 6

carbon atoms, or a straight-chain or branched-chain oxyalkylene group having 1 to 6 carbon atoms, X^2 is actually absent or a straight-chain or branched-chain alkylene group having 1 o 6 carbon atoms, R^6 represents a hydrogen atom or -NHY, wherein Y represents a hydrogen atom, an acyl group having 2 to 22 carbon atoms, an alkyl group having 1 to 22 carbon atoms, a hydroxyalkyl group having 1 to 22 carbon atoms, or a 3-alkoxy-2-hydoxypropyl group whose alkoxyl group is one having 1 to 22 carbon atoms, n represents an integer of 0 or 1, and R^5 represents a group represented by the following general Formula (2):



(2)

wherein X^3 represents -O- or $-NR^{10}-$, X^4 represents -O- or $-NR^{11}-$, R^7 represent a hydrogen atom, an amino acid side chain or a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms, R^8, R^{10}, and R^{11} represent each independently a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms, R^9 represents a hydrogen atom, an acyl group having 2 to 22 carbon atoms, an alkyl group having 1 to 22 carbon atoms, a hydroxyalkyl group having 1 to 22 carbon atoms, or a 3-alkoxy-2-hydroxypropyl group whose alkoxyl group is an alkoxy group having 1 to 22 carbon atoms, and m represents an integer of 0 or 1.

[Claim 2] The peptide derivatives or salts thereof as

set forth in Claim 1, wherein said Ar of the general Formula (1) represents a 1-naphthyl group or a 2-naphthyl group, said R^1, R^2 and R^3 of the general Formula (1) each represent a hydrogen atom, said R^4 of the general Formula (1) represents a basic amino acid side chain having an amino group or a guanidino group, said X^1 of the general Formula (1) is a methylene group, said X^2 of the general Formula (1) is actually absent, said R^6 of the general Formula (1) represents -NHY, wherein Y represents a hydrogen atom, an acyl group having 2 to 22 carbon atoms, an alkyl group having 1 to 22 carbon atoms, a hydroxyalkyl group having 1 to 22 carbon atoms, or a 3-alkoxy-2-hydoxypropyl group whose alkoxyl group is one having 1 to 22 carbon atoms, said n of the general Formula (1) represents an integer of 1, and said R^5 of the general Formula (1) represents a group represented by the general Formula (2), wherein said X^3 of the general Formula (2) represents -O- or -NH-, said X^4 of the general Formula (2) represents -O- or -NH-, said R^7 of the general formula (2) represents an amino acid side chain, a hydrogen atom, or a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms, said R^8 of the general Formula (2) represents a hydrogen atom, said R^9 of the general Formula (2) represents a hydrogen atom, an acyl group having 2 to 22 carbon atoms, an alkyl group having 1 to 22 carbon atoms, a hydroxyalkyl group having 1 to 22 carbon atoms, or a 3-alkoxy-2-hydroxypropyl group whose alkoxyl group is an alkoxyl group having 1 to 22 carbon atoms, and said m of the general Formula (2) represents an integer of 0 or 1.

[Claim 3] The peptide derivatives or salts thereof as set forth in Claim 1 or 2, wherein said peptide derivative represented by the general Formula (1) is D-1-naphthylalanyl-Arg-LeuNH$_2$, D-2-naphthylalanyl-Arg-LeuNH$_2$, L-1-naphthylalanyl-Arg-LeuNH$_2$ or L-2-naphthylalanyl-Arg-LeuNH$_2$.

[Claim 4] A melanocyte-stimulating hormone inhibitory compositions which comprises, as the active ingredient, at least one member selected from the group consisting of the peptide derivatives and salts thereof as set forth in any one of Claims 1 - 3.

[Claim 5] A whitening agent which comprises, as the active ingredient, at least one member selected from the group consisting of the peptide derivatives and the salts thereof as set forth in any one of Claims 1 - 3, or at the melanocyte-stimulating hormone inhibitory composition as set forth in Claim 4.

[Claim 6] An immunofunction controlling agent which comprises, as the active ingredient, at least one member selected from the group consisting of the peptide derivatives and the salts thereof as set forth in any one of Claims 1 - 3, or the melanocyte-stimulating hormone inhibitory composition as set forth in Claim 4.

[Claim 7] An appetite controlling agent which comprises, as the active ingredient, at least one member selected from the group consisting of the peptide derivatives and the salts thereof as set forth in any one of Claims 1 - 3,

or the melanocyte-stimulating hormone inhibitory composition as set forth in Claim 4.

[Claim 8] A cosmetic or external preparation for the skin which comprises, as the active ingredient, at least one member selected from the group consisting of the peptide derivatives and the salts thereof as set forth in any one of Claims 1 - 3, or the melanocyte-stimulating hormone inhibitory composition as set forth in Claim 4.

[Detailed Explanation of the Invention]

[0001]

[Technical Field to Which the Invention Partains]

The present invention relates to novel peptide derivatives having an inhibitory activity of melanocyte-stimulating hormone, and melanocyte-stimulating hormone inhibitory compositions, as well as to a whitening agent, an immunofunction regulator, an appetite regulator, a cosmetic or a skin preparation for external use, which comprises at least one of the said novel peptide derivatives.

[0002]

[Prior Art]

Melanocyte-stimulating hormone is known to participate in the control of the colors of the skin and hair of humans and animals, and to darken the color of the human skin (e.g., Nature (1961) 189, 176-179). It is reported as the main cause of such action that melanocyte-stimulating hormone accelerates the growth of melanocytes and also activates tyrosinase which is an enzyme for the biosynthesis of melanin (Proc. Natl. Acad.

Sci. (1995) 92, 1789-1793). On the other hand, it is known that melanocyte-stimulating hormone is produced by skin epidermal cells, and that the production amount is increased largely by the irradiation of ultraviolet rays (ACTH Relat. Rept. (1995) 6, 63-68). It is thought from these facts that melanocyte-stimulating hormone is the main cause of pigmentation after sunburn by ultraviolet rays.

[0003]

As other actions of melanocyte-stimulating hormone, there are known an inhibitory action of the production of nitrogen monoxide by macrophages and an immunosuppressive action through IL-10 (e.g., Immunology Today (1997) 18, 140-145) and an appetite-controlling action (e.g., Am. J. Physiol. 274 Endocrinol. Metab. 37 (1998) E627-E633).

[0004]

Accordingly, the suppression of the formation of melanocyte-stimulating hormone or the inhibition of the action thereof can realize the prevention of pigmentation to be caused by ultraviolet rays, the prevention, improvement or recovery of or from immune abnormality or immunodeficiency, or the regulation of body weight by appetite control.

[0005]

Hitherto, there have been known as melanocyte-stimulating hormone inhibitors, His-D-Arg-Ala-Trp-D-Phe-Lys-NH_2 (Peptides (1994) 15, 627-632), D-Trp-Arg-Leu-NH_2 (Proc. Natl. Acad. Sci. (1995) 92, 2894-2898), and the like. However, these inhibitors all

contain tryptophan which is an unstable amino acid, and therefore there is a problem that the stability during storage is inferior. Moreover, these inhibitors are known to decolor the skin of reptiles and the pigment cells of amphibians, but it has not been clarified whether they have the action of suppressing the formation of melanin and the activation of tyrosinase by melanocyte-stimulating hormone, which cause the pigmentation of the human skin.

[0006]

Moreover, as other melanocyte-stimulating hormone inhibitors, it is known that an agcuti protein and fragment peptides thereof have a pigmentation inhibitory action (WO 97/00892), but there are problems that the production thereof is not facile and that the stability during storage thereof is inferior.

[0007]

[Problems to be Solved by the Invention]

Under the circumstance of the prior art as has been described above, it is an object of the present invention is to provide novel peptide derivatives, which can inhibit the action of melanocyte-stimulating hormone, whereby the pigmentation can be prevented, can prevent, improve or recover from immune abnormality or immunodeficiency, or regulate body weight by appetite control, and also can be used as cosmetics or external preparations for the skin, and in addition, can be produced easily, and are excellent in the stability during storage.

[0008]

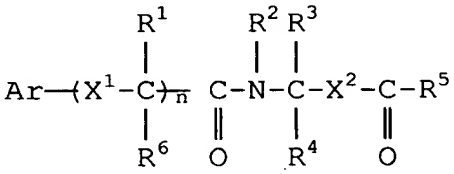
[Means for Solving the Problems]

As a result of the extensive studies for attaining the above object, the present inventors have found that it can be attained with novel peptide derivatives represented by the following general formula (1) or salts thereof, and accomplished the present invention based on such findings.

[0009]

Accordingly, the present invention relates to di- or tripeptide derivatives having a naphthyl group and represented by the following general formula (1) or salts thereof.

[0010]



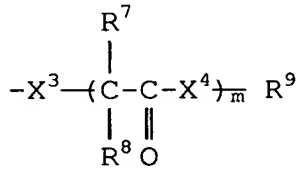
(1)

[0011]

wherein Ar represents a naphthyl group which may have substituent(s), R^1, R^2 and R^3 represent each independently a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms which may have substituent(s), R^4 represents a hydrogen atom, an amino acid side chain, an amino group, an amidino group, a guanidinyl group, a straight-chain or branched-chain aminoalkyl group having 1 to 6 carbon atoms, a straight-chain or branched-chain amidinoalkyl group having 1 to 6 carbon atoms, a straight-chain or branched-chain

guanidinoalkyl group having 1 to 6 carbon atoms, or an amidinoaryl group having 6 to 12 carbon atoms, all of which group may have substituent(s), X^1 is actually absent (i.e., nothing) or an alkylene group having 1 or 6 carbon atoms, an aminoalkylene group having 1 to 6 carbon atoms which may have as a substituent a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms, or a straight-chain or branched-chain oxyalkylene group having 1 to 6 carbon atoms, X^2 is actually absent or a straight-chain or branched-chain alkylene group having 1 o 6 carbon atoms, R^6 represents a hydrogen atom or -NHY, wherein Y represents a hydrogen atom, an acyl group having 2 to 22 carbon atoms, an alkyl group having 1 to 22 carbon atoms, a hydroxyalkyl group having 1 to 22 carbon atoms, or a 3-alkoxy-2-hydoxypropyl group having an alkoxyl group having 1 to 22 carbon atoms, n represents an integer of 0 or 1, and R^5 represents a group represented by the following general formula (2):

[0012]



(2)

[0013]

wherein X^3 represents -O- or $-NR^{10}-$, X^4 represents -O- or $-NR^{11}-$, R^7 represents a hydrogen atom, an amino acid side chain or a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms, R^8, R^{10}, and R^{11} represent each independently a

hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms, R^9 represents a hydrogen atom, an acyl group having 2 to 22 carbon atoms, an alkyl group having 1 to 22 carbon atoms, a hydroxyalkyl group having 1 to 22 carbon atoms, or a 3-alkoxy-2-hydroxypropyl group whose alkoxyl group is an alkoxy group having 1 to 22 carbon atoms, and m represents an integer of 0 or 1.

[0014]

It is to be noted that the peptide derivatives represented by the above general formula (1) are novel compounds which have not been described in the literature.

[0015]

Furthermore, the present invention relates to a melanocyte-stimulating hormone inhibitory composition, a whitening agent, an immunofunction regulator, an appetite regulator, a cosmetic or a skin preparation for external use, which comprises, as the active ingredient, at least one selected from the peptide derivatives represented by the above general formula (1) or salts thereof.

[0016]

[Embodiment of the Invention]

In the following will be described the present invention in greater detail.

[0017]

In the peptide derivatives of the present invention represented by the general formula (1) and salts thereof, R^6 is defined as described above, and specific examples of Y in

the case where R^6 is NHY, include, e.g., a hydrogen atom, an acetyl group, propioyl group, isopropioyl group, n-butyroyl group, isobutyroyl group, sec-butyroyl group, tert-butyroyl group, n-amyloyl group, sec-amloyl group, tert-amyloyl group, isoamyloyl group, n-hexyloyl group, cyclohexyloyl group, n-heptanoyl group, n-octanoyl group, 2-ethylhexyloyl group, nonyoyl group, isononyoyl group, decanoyl group, isodecanoyl group, undecanoyl group, lauroyl group, tridecanoyl group, isotridecanoyl group, myristoyl group, palmitoyl group, isopalmitoyl group, stearoyl group, isostearoyl group, oleoyl group, docosanoyl group, methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-amyl group, sec-amyl group, tert-amyl group, isoamyl group, n-hexyl group, cyclohexyl group, n-heptyl group, n-octyl group, 2-ethylhexyl group, nonyl group, isononyl group, decyl group, isodecyl group, undecyl group, lauryl group, tridecyl group, isotridecyl group, myristyl group, cetyl group, isocetyl group, stearyl group, isostearyl group, oleyl group, behenyl group, 2-hydroxyethyl group, 2-hydroxypropyl group, 2-hydroxyisopropyl group, 2-hydroxy-n-butyl group, 2-hydroxyisobutyl group, 2-hydroxy-sec-butyl group, 2-hydroxy-tert-butyl group, 2-hydroxy-n-amyl group, 2-hydroxy-sec-amyl group, 2-hydroxy-tert-amyl group, 2-hydroxyisoamyl group, 2-hydroxy-n-hexyl group, 2-hydroxycyclohexyl group, 2-hydroxy-n-heptyl group, 2-hydroxy-n-octyl group, 2-hydroxy-2-ethylhexyl group,

2-hydroxynonyl group, 2-hydroxyisononyl group, 2-hydroxydecyl group, 2-hydroxyisodecyl group, 2-hydroxyundecyl group, 2-hydroxylauryl group, 2-hydroxytridecyl group, 2-hydroxyisotridecyl group, 2-hydroxymyristyl group, 2-hydroxycetyl group, 2-hydroxyisocetyl group, 2-hydroxystearyl group, 2-hydroxyisostearyl group, 2-hydroxyoleyl group, 2-hydroxybehenyl group, 3-methoxy-2-hydroxypropyl group, 3-ethoxy-2-hydroxypropyl group, 3-propoxy-2-hydroxypropyl group, 3-isopropoxy-2-hydroxypropyl group, 3-n-butoxy-2-hydroxypropyl group, 3-isobutoxy-2-hydroxypropyl group, 3-sec-butoxy-2-hydroxypropyl group, 3-tert-butoxy-2-hydroxypropyl group, 3-n-amyloxy-2-hydroxypropyl group, 3-sec-amyloxy-2-hydroxypropyl group, 3-tert-amyloxy-2-hydroxypropyl group, 3-isoamyloxy-2-hydroxypropyl group, 3-n-hexyloxy-2-hydroxypropyl group, 3-cyclohexyloxy-2-hydroxypropyl group, 3-n-heptyloxy-2-hydroxypropyl group, 3-n-octyloxy-2-hydroxypropyl group, 3-(2-ethylhexyl)oxy-2-hydroxypropyl group, 3-nonyloxy-2-hydroxypropyl group, 3-isononyloxy-2-hydroxypropyl group, 3-decyloxy-2-hydroxypropyl group, 3-isodecyloxy-2-hydroxypropyl group,

3-undecyloxy-2-hydroxypropyl group,

3-lauryloxy-2-hydroxypropyl group,

3-tridecyloxy-2-hydroxypropyl group,

3-isotridecyloxy-2-hydroxypropyl group,

3-myristyloxy-2-hydroxypropyl group,

3-cetyloxy-2-hydroxypropyl group,

3-isocetyloxy-2-hydroxypropyl group,

3-stearyloxy-2-hydroxypropyl group,

3-isostearyloxy-2-hydroxypropyl group,

3-oleyloxy-2-hydroxypropyl group,

3-behenyloxy-2-hydroxypropyl group, and the like.

[0018]

The position where Ar and X^1, both defined as above, are bonded to each other, is not particularly limited and any position may be optionally selected. And, the hydrogen atom(s) of these groups bonded to the aromatic ring may be replaced by one or more of halogen atoms, alkyl groups having 1 to 6 carbon atoms, hydroxyl groups, hydroxyalkyl groups having 1 to 6 carbon atoms, nitro groups, alkoxyl groups having 1 to 6 carbon atoms groups or carboxyl groups, or sulfonic acid. In the case where the hydrogen atoms are replaced by two or more groups, the two or more substituents may be the same or different.

[0019]

As the mother skeleton of Ar, there may be mentioned 1-naphthyl group or 2-naphthyl group.

[0020]

As specific examples of R^4 defined as above, there may

be mentioned amino acid side chains (by amino acid side chain being meant a residue resulting from the removal of $C(COOH)NH_2$ from an amino acid) derivable from acidic amino acids such as glutamic acid, aspartic acid, cysteic acid, homocysteic acid, and the like, neutral amino acids such as alanine, β-alanine, 2-aminobutyric acid, valine, norvaline, leucine, norleucine, isoleucine, phenylalanine, phenylglycine, threonine, serine, homoserine, tyrosine, dopa, cysteine, methionine, glutamine, asparagine, and the like, and basic amino acids such as lysine, homolysine, ornithine, arginine, homoarginine, histidine, and the like; or a hydrogen atom. Among these, more preferred are the side chains derivable from basic amino acids. Other than the side chains derivable from the amino acids, there may be mentioned amidinoethyl, amidinopropyl, amidinobutyl, amidinopentyl, amidinohexyl, amidinophenyl, and the like, having an amidino group.

[0021]

Specific examples of R^7 in the general formula (2) defined as above include, e.g., amino acid side chains derivable from acidic amino acids such as glutamic acid, aspartic acid, cysteic acid, homocysteic acid, and the like, neutral amino acids such as alanine, β-alanine, 2-aminobutyric acid, valine, norvaline, leucine, norleucine, isoleucine, phenylalanine, phenylglycine, tryptophan, threonine, serine, homoserine, tyrosine, dopa, cysteine, methionine, glutamine, asparagine, and the like, and basic amino acids such as lysine, homolysine, ornithine, arginine, homoarginine, histidine and the like; or

a hydrogen atom. Among these, more preferred are the amino acid side chains derivable from neutral amino acids having a hydrophobic side chain.

[0022]

Specific examples of R^9 defined as above include, e.g., a hydrogen atom, a methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-amyl group, sec-amyl group, tert-amyl group, isoamyl group, n-hexyl group, cyclohexyl group, n-heptyl group, n-octyl group, 2-ethylhexyl group, nonyl group, isononyl group, decyl group, isodecyl group, undecyl group, lauryl group, tridecyl group, isotridecyl group, myristyl group, cetyl group, isocetyl group, stearyl group, isostearyl group, oleyl group, behenyl group, 2-hydroxyethyl group, 2-hydroxypropyl group, 2-hydroxyisopropyl group, 2-hydroxy-n-butyl group, 2-hydroxyisobutyl group, 2-hydroxy-sec-butyl group, 2-hydroxy-tert-butyl group, 2-hydroxy-n-amyl group, 2-hydroxy-sec-amyl group, 2-hydroxy-tert-amyl group, 2-hydroxyisoamyl group, 2-hydroxy-n-hexyl group, 2-hydroxycyclohexyl group, 2-hydroxy-n-heptyl group, 2-hydroxy-n-octyl group, 2-hydroxy-2-ethylhexyl group, 2-hydroxynonyl group, 2-hydroxyisononyl group, 2-hydroxydecyl group, 2-hydroxyisodecyl group, 2-hydroxyundecyl group, 2-hydroxylauryl group, 2-hydroxytridecyl group, 2-hydroxyisotridecyl group, 2-hydroxymyristyl group, 2-hydroxycetyl group, 2-hydroxyisocetyl group,

2-hydroxystearyl group, 2-hydroxyisostearyl group,
2-hydroxyoleyl group, 2-hydroxybehenyl group,
3-methoxy-2-hydroxypropyl group, 3-ethoxy-2-hydroxypropyl group, 3-propoxy-2-hydroxypropyl group,
3-isopropoxy-2-hydroxypropyl group,
3-n-butoxy-2-hydroxypropyl group,
3-isobutoxy-2-hydroxypropyl group,
3-sec-butoxy-2-hydroxypropyl group,
3-tert-butoxy-2-hydroxypropyl group,
3-n-amyloxy-2-hydroxypropyl group,
3-sec-amyloxy-2-hydroxypropyl group,
3-tert-amyloxy-2-hydroxypropyl group,
3-isoamyloxy-2-hydroxypropyl group,
3-n-hexyloxy-2-hydroxypropyl group,
3-cyclohexyloxy-2-hydroxypropyl group,
3-n-heptyloxy-2-hydroxypropyl group,
3-n-octyloxy-2-hydroxypropyl group,
3-(2-ethylhexyl)oxy-2-hydroxypropyl group,
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3-tridecyloxy-2-hydroxypropyl group,
3-isotridecyloxy-2-hydroxypropyl group,
3-myristyloxy-2-hydroxypropyl group,

3-cetyloxy-2-hydroxypropyl group,

3-isocetyloxy-2-hydroxypropyl group,

3-stearyloxy-2-hydroxypropyl group,

3-isostearyloxy-2-hydroxypropyl group,

3-oleyloxy-2-hydroxypropyl group,

3-behenyloxy-2-hydroxypropyl group, and the like.

[0023]

The residue of each amino acid of the peptide derivatives represented by the above general formula (1) may be either optically active one or racemic one.

[0024]

Specific examples of the salts of the compounds represented by the above general formula (1) include physiologically acceptable salts, for example, inorganic salts, e.g., those of alkali metals such as sodium, potassium and the like, those of alkaline earth metals such as magnesium, calcium and the like, ammonium salts, and the like; organic amine salts, e.g., those of monoethanolamine, diethanolamine, triethanolamine, 2-amino-2-methyl-1-propanol, 2-amino-2-methyl-1,3-propanediol, lysine, ornithine, arginine and the like; halogen salts, e.g., those of chlorine, bromine, iodine and the like; inorganic acid salts, e.g., hydrochloride, sulfate, carbonate, phosphate and the like; organic acid salts, e.g., acetates, trifluoroacetates, tartrates, citrates, p-toluenesulfonates, glycolates, malates, lactates, fatty acid salts, acidic amino acid salts and pyroglutamates; and the like. Two or more of these salts

may be used in combination.

[0025]

The peptide derivatives of the present invention represented by the above general formula (1) can be synthesized, for example, as follows. First, a protected basic amino acid and a neutral amino acid whose carboxyl group has been amidated are condensed with a water-soluble carbodiimide in methylene chloride, and successive treatment such as acid treatment affords a protected dipeptide wherein only the protective group on the main chain has been removed. Next, the protected dipeptide and an N-terminal protected amino acid derivative having an aryl group such as naphthylmethyl group or the like on the side chain are condensed with a water-soluble carbodiimide in methylene chloride, and the protective group of the resulting protected tripeptide is removed by, for example, reduction in the presence of palladium-carbon catalyst, whereby an aimed-at peptide derivative is obtained. Further, various derivatives wherein the N-terminal amino group is acylated, alkylated, hydroxyalkylated or 3-alkoxy-2-hydroxypropylated, can be obtained by, for example, reacting a protected tripeptide whose N-terminal is only deprotected, with an acid anhydride, an acid chloride, an alkyl halide, an epoxyalkane or an alkyl glycidyl ether, followed by reductive deprotection in the presence of palladium-carbon catalyst, and the like.

[0026]

Moreover, a tripeptide whose C-terminal is a carboxyl

group can be obtained by catalytic reduction of a tripeptide similarly obtained using a neutral amino acid whose carboxyl group is protected with a benzyl group instead of the neutral amino acid whose carboxyl group is amidated. Furthermore, various derivatives can be obtained by subjecting an N-terminal amino group to acylation, alkylation, hydroxyalkylation or 3-alkoxy-2-hydroxypropylation in a step precedent to the step of removing the benzyl group which is a protective group of the basic amino acid side chain or a protective group of the carboxyl group, and successive catalytic reduction. Furthermore, dehydrative condensation of the peptide derivatives with an alcohol in the presence of an acid catalyst affords various C-terminal carboxylic ester derivatives.

[0027]

In addition, a derivative whose C-terminal carboxyl group is esterified or amidated can be obtained by dehydrative condensation of a tripeptide whose C-terminal is a carboxyl group and whose amino group on the mian chain and basic amino acid side chain have been protected, with an alkylamine or addition reaction of the tripeptide with an epoxyalkane or an alkyl glycidyl ether, followed by similar successive catalytic reduction.

[0028]

The melanocyte-stimulating hormone inhibitory composition, whitening agent, immunofunction controlling agent, appetite controlling agent, cosmetic and external preparation for the skin of the present invention, which

comprise, as the active ingredient, a peptide derivative which is the novel compound of the present invention, may be prepared optionally as those for oral or parenteral administration. For the purpose of allowing the same to act on the skin, they may be prepared in such dosage form that they may be directly administered on the skin by, e.g., application. In this case, they are prepared by incorporating into a cosmetic or an external preparation for the skin, at least one selected from the peptides of the present invention and salts thereof.

[0029]

In these cases, at least one selected from the novel peptide derivatives and salts thereof of the present invention may be appropriately incorporated into a cosmetic usually in an amount of 0.01 to 10% by weight, preferably 0.1 to 5% by weight, relative to the total amount of the cosmetic. Into an external preparation for the skin of the present invention, said at least one selected from the novel peptide derivatives and salts thereof of the present invention is properly incorporated usually in an amount of 0.01 to 50% by weight, preferably 0.1 to 20% by weight. When the amount is less than 0.01% by weight, the effect caused by the addition is not exhibited and therefore, such amount is not preferable. Whereas, when the amount is more than 50% by weight, there may be problems of feeling upon the use such as occurrence of creaky feeling toward the skin and therefore, such amount is not preferable either.

[0030]

When at least one selected from the peptide derivatives

and salts thereof of the present invention is used by incorporating the same into a cosmetic or an external preparation for the skin, ingredients generally used in cosmetics or external preparations for the skin may be added within the amount range where the effects intended by the present invention are not inhibited. As examples of ingredients generally used in cosmetics or external preparations for the skin, there may be mentioned oily materials, surfactants, solvents, moisture keeping agents, polymeric substances, powdery substances, pigments, perfumes, other conventional ingredients, and the like.

[0031]

The oily materials include oils and fats such as animal and vegetable oils, and the like, waxes such as lanolin, and the like, hydrocarbons such as paraffin, and the like, higher alcohols such as cetanol, and the like, higher fatty acids such as stearic acid, and the like, sterols, phospholipids such as lecithin, and the like, synthetic esters of myristic acid, and the like, metal soaps, silicone oils, and the like.

[0032]

The surfactants include anionic surfactants, cationic surfactants, amphoteric surfactants, nonionic surfactants, emulsifying or solubilizing agents, and the like.

[0033]

The solvents include lower alcohols such as ethanol, and the like, ethers, glycerols, liquid nonionic surfactants, liquid oily materials, other organic solvents, water, and the

like.

[0034]

The moisture keeping agents include polyhydric alcohols such as glycerol, and the like, salts of organic acids such as pyrrolidonecarboxylic acid, and the like, urea, mucopolysaccharides such as hyaluronic acid, and the like, salts of amino acids such as proline, and the like, and the like.

[0035]

The polymeric substances include natural polymeric compounds such as collagen, and the like, semi-synthetic polymeric compounds such as partially deacetylated chitin, and the like, synthetic polymeric compounds such as carboxymethyl cellulose, and the like, and the like.

[0036]

The powdery substances include inorganic pigments such as talc, and the like, functional pigments such as synthetic mica, and the like, hybrid fine powder, pearl-glossy pigments such as titanium dioxide-covered mica, and the like, photochromic pigments, polymeric powders such as nylon powder, and the like, organic powders such as N^{ε}-lauroyllysine, and the like, and the like.

[0037]

The pigments include the first class of the Japanese statutory tar pigments, the second class of the Japanese statutory tar pigments, the third class of the Japanese statutory tar pigments, hair dyes, natural pigments, mineral pigments, and the like.

[0038]

The perfumes include animal perfumes such as musk, and the like, vegetable perfumes such as jasmine, and the like, synthetic perfumes such as α-amylcinnamaldehyde, and the like, blended perfumes, and the like.

[0039]

The other conventional ingredients for cosmetics or external preparations for the skin include antiseptics/disinfectants, antioxidants, UV absorbers, chelating agents, antifading agents, buffering agents, medicines for acne, antiscurf and antiitch agents, antiperspirant deodorant, medicines for burns, acaricides/pediculicides, keratin softeners, medicines for xeroderma, antivirus agents, transdermal absorption promoting agents, hormones, vitamins, amino acids/peptides, proteins, astringents, anti-inflammatory agents, refrigerants/irritants, ingredients derived from animals or vegetables, melanin synthesis inhibitors (whitening agents), antibiotics, antifungal agents, hair growth agents, and the like.

[0040]

The melanocyte-stimulating hormone inhibitory composition, whitening agent, immunofunction controlling agent, appetite controlling agent, cosmetic and external preparation for the skin of the present invention are not particularly limited in their dosage form, and they may take suitable dosage forms such as solutions, pastes, gels, solids,

granules, powders, capsules, aerosols, and the like. More specifically, they may be used in the dosage form of oils, lotions, creams, milky lotions, gels, shampoos, hair rinses, hair conditioners, enamels, foundations, lipsticks, face powders, packs, ointments, tablets, injections, granules, capsules, perfumes, powders, eau de Colognes, tooth pastes, soaps, aerosols, cleansing foams, and the like.

[0041]

The melanocyte-stimulating hormone inhibitory compositon, whitening agent, immunofunction controlling agent, appetite controlling agent, cosmetic and external preparation for the skin, of the present invention can be used as agents for preventing or improving skin ageing, agents for preventing or improving skin inflammation, bath agents, hair growth agents, skin care solutions, anti-sunburn agents, agents for preventing or improving hyperesthesia optica such as xeroderma pigmentosum, solar urticaria, and the like, agents for preventing or improving photoallergy, agents for preventing or improving photoimmunosuppression, or agents for preventing or improving skin roughness due to trauma, chaps and cracks, and the like.

[0042]

Furthermore, the melanocyte-stimulating hormone inhibitory compositon or whitening agent of the present invention is useful for preventing or improving pigmentation by ultraviolet rays, and for preventing or improving chloasma, ephelides and senile pigment freckle.

[0043]

Moreover, the melanocyte-stimulating hormone inhibitory composition of the present invention can be used as agents for preventing or treating various diseases in which melanocyte-stimulating hormone participates, such as immune abnormality or immunodeficiency, or for the purpose of the regulation of body weight by appetite control.

[0044]

[Examples]

In the following will be described the present invention more specifically with reference to the examples, but the present invention is not limited these examples.

[0045]

By the way, in the following examples, the incorporated amounts are represented in terms of % by weight, and naphthylalanyl group or naphthylalanine is abbreviated as Nal.

[0046]

Synthetic Example 1: D-1-Nal-Arg-LeuNH_2

Boc-Arg(Z)2(5 g, 9.22 mmol) was dissolved in methylene chloride (75 ml), and under ice-cooling, water-soluble carbodiimide hydrochloride (1.77 g, 9.22 mmol) and HOBt (1-hydroxybenzotriazole, 1.25 g, 9.22 mmol) were added thereto. Then, a methylene chloride solution (75 ml) of LeuNH_2 hydrochloride (1.61 g, 9.68 mmol) and triethylamine (1.91 g, 18.9 mmol) was added dropwise thereto over a period of 10 minutes, and the mixture was heated back to room temperature, followed by stirring overnight. The reaction liquid was

concentrated under reduced pressure and then, ethyl acetate was added to the residue. The mixture was washed with 5% citric acid, 5% sodium hydrogen carbonate, and saturated saline, successively. After drying over magnesium sulfate, drying under reduced pressure afforded Boc-Arg(Z)2-LeuNH$_2$ (5.8 g, 8.86 mmol).

[0047]

A portion of the resulting Boc-Arg(Z)2-LeuNH$_2$ (2 g, 3.1 mmol) was treated with trifluoroacetic acid (10 ml), whereby Arg(Z)2-LeuNH$_2$ (1.28 g, 2.3 mmol) was obtained. Then, the resulting Arg(Z)2-LeuNH$_2$ (1.28 g, 2.3 mmol) and Z-D-1-Nal (0.803 g, 2.3 mmol) were similarly condensed, whereby Z-D-1-Nal-Arg(Z)2-LeuNH$_2$ (1.63 g, 1.84 mmol) was obtained. Next, the resulting Z-D-1-Nal-Arg(Z)2-LeuNH$_2$ (1.63 g, 1.84 mmol) was dissolved in methanol (1,000 ml) and reduced in the presence of palladium-carbon catalyst, whereby D-1-Nal-Arg-LeuNH$_2$ (0.80 g, 1.66 mmol) was obtained.

[0048]

Synthesis Example 2: D-2-Nal-Arg-LeuNH$_2$

Synthesis Example 1 was repeated except that Z-D-2-Nal was used instead of Z-D-1-Nal, whereby D-2-Nal-Arg-LeuNH$_2$ was obtained.

[0049]

Synthesis Example 3: L-1-Nal-Arg-LeuNH$_2$

Synthesis Example 1 was repeated except that Z-L-1-Nal was used instead of Z-D-1-Nal, whereby L-1-Nal-Arg-LeuNH$_2$ was obtained.

[0050]

Synthesis Example 4: L-2-Nal-Arg-LeuNH$_2$

Synthesis Example 1 was repeated except that Z-L-2-Nal was used instead of Z-D-1-Nal, whereby L-2-Nal-Arg-LeuNH$_2$ was obtained.

[0051]

The results by the mass spectrometry (ESI-MS) of the compounds obtained by the above Synthesis Examples will be shown in the following Table 1.

[0052]

Table 1: ESI mass spectra

Synthesis Example	Compounds	Molecular weight	
		Calcd.	Found(MH+)
1	D-1-Nal-Arg-LeuNH$_2$	483	484
2	D-2-Nal-Arg-LeuNH$_2$	483	484
3	L-1-Nal-Arg-LeuNH$_2$	483	484
4	L-2-Nal-Arg-LeuNH$_2$	483	484

[0053]

Test Example 1: Test on inhibition against melanocyte-stimulating hormone receptor

B16 melanoma cells were inoculated to a 12-well plate in an amount if 1×10^4 per 1 well in terms of cell number and cultured at 37°C in the presence of 50 % CO_2 for 48 hours. After culturing, the plate was washed with a non-serum medium (D-MEM medium not containing serum) in an amount of 1 ml per 1 well. Then, a non-serum medium containing 1 mM 3-isobutyl-1-methylxanthine, 10 nM α-MSHC

(melanocyte-stimulating hormone) and one test compound (selected from the group consisting of D-1-Nal-Arg-LeuNH$_2$, D-2-Nal-Arg-LeuNH$_2$ and L-1-Nal-Arg-LeuNH$_2$) having a different concentration was added in an amount of 1 ml per 1 well and incubated at 37°C for 5 minutes. After incubating, the medium was completely removed from the plate and thereto was added an ice-cooled 2.5% perchloric acid in a precise amount of 1 ml. It was, as it was, incubated with ice cooling for 30 minutes, whereby the cAMP was extracted from within the cells. After incubating, the extract was neutralized by adding 90 ml per 1 well, of 4.2 M potassium hydroxide. The neutralized extract was centrifuged at 12,000 rpm at 4°C for 10 minutes, and the amount of the cAMP present in the supernatant was measured by Biotrak cAMP EIA System (ex Pharmacia, Amasham). All the test compounds almost completely inhibited at 1 mM the cAMP production within the cells by 10 mM MSH stimulation. In Table 2 will be shown 50% inhibitory concentration (IC 50) of each test compound against cAMP production with 10 nM MSH. As shown in the table, the test compounds inhibited effectively the cAMP increasing action by melanocyte-stimulating hormone.

[0054]

Table 2: Test on inhibition against melanocyte-stimulating hormone

Test Compound	50% inhibitory Concentration (IC50, nM)
D-1-Nal-Arg-LeuNH$_2$	540
D-2-Nal-Arg-LeuNH$_2$	42
L-1-Nal-Arg-LeuNH$_2$	470
D-Trp-Arg-LeuNH$_2$	230

[0055]

Test Example 2: Test on suppression of the melanin formation caused by human melanocytes

Human melanocytes in logarithmic growth phase were treated with trypsin and inoculated to a 6-well plate with "Medium 154s" (manufactured by Kurabo Industries Ltd., containing a growth factor (HMGS)), in an amount of 1.5×10^5 per 1 well in terms of cell number. The cells were cultured at 37°C in a carbon dioxide incubator, the CO_2 concentration being 5%, for 1 day. Thereafter, rinsing was carried out with the use of HBS (Hepes Buffer Saline), followed by medium replacement with "MCDB153" (containing fetal bovine serum, insulin, b-FGF, transferrin, and tocopherol), and followed by culturing for further 2 days. A whitening agent (a compound to be tested) was adjusted with "MCDB153" (containing fetal bovine serum, insulin, b-FGF, transferrin, and tocopherol) + α-MSH in such way that the concentration would be 200 μM, 20 μM, or 2 μM, and was added to the 6-well plate. Also, a further

6-well plate culture was carried out with the use of "MCDB153" (containing fetal bovine serum, insulin, b-FGF, transferrin, and tocopherol) +α-MSH without the whitening agent, and still further a 6-well plate culture was carried out with the use of "MCDB153" (containing fetal bovine serum, insulin, b-FGF, transferrin, and tocopherol) alone, at the same time. The medium replacement with the above "MCDB153" (containing fetal bovine serum) containing a whitening agent was carried out twice every 2 days.

[0056]

After the first addition of the whitening agent, the effect of suppressing the melanin formation was confirmed on the 6th day. Namely, the medium on each 6-well plate was removed by suction, and the wells were rinsed with HBS. Thereafter, the 6-well plate was air-dried, and 1/5M NaOH (230 μl) was added to the wells to dissolve the melanin out of the melanocytes. The solution (200 μl) was evaluated by Abs (absorbance) on a microplate reader (475 nm). The suppression rate of the melanin formation by each compound tested was calculated according to the following equation (1). The results will be shown below in Table 3.

[0057]

The suppression rate of the melanin formation (%)

$$= \{1-(A_1 - A_3)/(A_2 - A_3)\} \times 100 \qquad (1)$$

A_1: absorbance at 475 nm when both of the compound to be tested and MSH were added.

A_2: absorbance at 475 nm when the compound to be tested

was not added and MSH was added.

A_3: absorbance at 475 nm when both of the compound to be tested and MSH were not added.

[0058]

Table 3: Test on suppression of the melanin formation

Compounds tested	Addition concentration (μM)	Suppression rate (%)
D-1-Nal-Arg-LeuNH$_2$	20	43
	200	52
D-2-Nal-Arg-LeuNH$_2$	2	49
	20	51
	200	70
L-1-Nal-Arg-LeuNH$_2$	20	8
	200	28
D-Trp-Arg-LeuNH$_2$	20	24
	200	57

[0059]

As is shown in Table 3, the test compounds suppressed effectively the melanin formation by the melanocytes, increased by the addition of the melanocyte-stimulating hormone. It can be understood from this that the test compounds have an inhibitory activity of the melanin formation induced by melanocyte stimulating hormone.

[0060]

Test Example 3: Test of stability during storage

An aqueous 0.1% solution of D-2-Nal-Arg-LeuNH$_2$ of the present invention, and that of D-Trp-Arg-LeuNH$_2$ which is a known melanocyte-stimulating hormone inhibitor were prepared and

stored at 4°C for 6 months, respectively. The stability during storage was evaluated by comparing the degree of coloring with standard colors of APHA (American Public Healthy Association) method. The results will be shown in the following Table 4.

[0061]

Table 4: Test of stability during storage

	Compounds tested	Degree of coloring (APHA Standard color)
Example	D-2-Nal-Arg-LeuNH$_2$	20
Comparative Example	D-Trp-Arg-LeuNH$_2$	200

[0062]

As is shown in Table 4, D-2-Nal-Arg-LeuNH$_2$ of the present invention showed an APHA value of 20 and was almost not colored, whereas D-Trp-Arg-LeuNH$_2$, a known melanocyte-stimulating hormone inhibitor showed an APHA value of 200 and was much colored. It can be understood from this, that D-2-Nal-Arg-LeuNH$_2$ of the present invention has a good stability.

[0063]

The above test results will be summarized in the following Table 5.

[0064]

Table 5: Evaluation results of MSH inhibitors

Test compounds	MSH inhibitory activity	Melanin formation suppressing activity	Stability during storage
D-1-Nal-Arg-LeuNH$_2$	B	B	Not carried out
D-2-Nal-Arg-LeuNH$_2$	A	A	A
L-1-Nal-Arg-LeuNH$_2$	B	B	Not carried out
D-Trp-Arg-LeuNH$_2$	B	B	C

The standards of the evaluations in Table 5 are as follows:

(1) MSH inhibitory activity:

50% Inhibitory concentration in the test	Evaluation
100 nM or less	A
101 to 1000 nM	B
1001 nM or more	C

(2) Melanin formation suppressing activity:

Minimum concentration showing melanin formation suppressing activity in the test	Evaluation
1 to 10 μM	A
11 to 100 μM	B
101 μM or more	C

(3) Test on stability during storage:

Degree of coloring in the test (APHA standard colors)	Evaluation
20 or less	A
21 to 100	B
101 or more	C

[0065]

From the above table, it can be understood that the compounds of the present invention are advantageous as a whole.

[0066]

Melanocyte-stimulating hormone inhibitory compositions, cosmetics or skin preparations for external use were prepared in an ordinary way in accordance with the formulations indicated in the following Formulation Examples 1 - 11.

[0067]

Formulation Example 1: Tablet	wt%
D-2-Nal-Arg-LeuNH$_2$	10
Milk sugar	50
Starch	20
Carboxymethyl cellulose	19
Magnesium stearate	1

[0068]

Formulation Example 2: Injection	wt%
D-2-Nal-Arg-LeuNH$_2$	0.1
Grape sugar	2.0
Injection water	balance

[0069]

Formulation Example 3: Ointment	wt%
N-Lauroyl-D-2-Nal-Arg-LeuNH$_2$	1.0
Urea	20.0
White vaseline	15.0
Light liquid paraffin	6.0
Cetanol	3.0
Stearyl alcohol	3.0
Glycerol monostearate	5.0
Perfume	proper amount
Preservative	proper amount
Buffer	1.0
Purified water	balance

[0070]

Formulation Example 4: Cream	wt%
D-2-Nal-Arg-LeuOEt	1.0
Kojic acid	1.0
Stearic acid	2.0
Poly(oxyethylene)(25)cetyl ether	3.0
Glycerol monostearate	2.0
Octyl dodecanol	10.0
Cetanol	6.0
Reduced lanolin	4.0
Squalane	9.0
1,3-Butylene glycol	6.0
Polyethylene glycol (1500)	4.0
Preservative	proper amount
Perfume	proper amount
Purified water	balance

[0071]

Formulation Example 5: Cream	wt%
D-2-Nal-Arg-LeuOEt	1.0
Arbutin	1.0
Stearic acid	2.0
Poly(oxyethylene)(25)cetyl ether	3.0
Glycerol monostearate	2.0
Octyl dodecanol	10.0
Cetanol	6.0
Reduced lanolin	4.0
Squalane	9.0
1,3-Butylene glycol	6.0
Polyethylene glycol (1500)	4.0
Preservative	proper amount
Perfume	proper amount
Purified water	balance

[0072]

Formulation Example 6: Milky lotion	wt%
D-1-Nal-Arg-LeuNH$_2$	2.0
Retinol	0.1
Beeswax	0.5
Vaseline	2.0
Glycerol monostearate	1.0
Polyethylene glycol monooleate	1.0
Methylpolysiloxane	2.0
Cetanol	1.0
Squalane	6.0
Carboxyvinyl polymer	0.5
1,3-Butylene glycol	4.0
Ethanol	5.0
Preservative	proper amount
Perfume	proper amount
Purified water	balance

[0073]

Formulation Example 7: Gel	wt%
N-Acetyl-D-1-Nal-Arg-LeuNH$_2$	0.05
Liquid paraffin	12.0
Glycerol tri(2-ethylhexanoate)	50.0
Sorbit	10.0
Polyethylene glycol(400)	5.0
Acylmethyltaurine	5.0
Poly(oxyethylene)(20)isocetyl ether	10.0
Preservative	proper amount
Perfume	proper amount
Purified water	balance

[0074]

Formulation Example 8: Cosmetic liquid	wt%
D-2-Nal-Arg-LeuNH$_2$	0.5
Dipropylene glycol	5.0
Polyethylene glycol(400)	5.0
Ethanol	10.0
Carboxyvinyl polymer	0.5
Sodium alginate	0.5
Potassium hydroxide	0.2
Poly(oxyethylene)(20)sorbitan monostearate	1.0
Sorbit monooleate	0.5
Oleyl alcohol	0.5
Placenta extract	0.2
dl-α-tocophenol acetate	0.2
Perfume	proper amount
Preservative	proper amount
Anti-fading agent	proper amount
Purified water	balance

[0075]

Formulation Example 9: Pack	wt%
L-1-Nal-Arg-LeuNH$_2$	3.0
Poly(vinyl alcohol)	15.0
Carboxymethyl cellulose	5.0
1,3-Butylene glycol	5.0
Ethanol	12.0
Poly(oxyethylene)(20)oleyl ether	0.5
Perfume	proper amount
Preservative	proper amount
Buffer	proper amount
Purified water	balance

[0076]

Formulation Example 10: Foundation	wt%
N-Lauroyl-L-1-Nal-Arg-LeuNH$_2$	5.0
Liquid paraffin	10.0
Poly(oxyethylene)(20)sorbitan monostearate	3.5
Propylene glycol	3.0
Titanium oxide	9.0
Kaolin	24.0
Talc	42.0
Coloring pigment	3.0
Preservative	proper amount
Perfume	proper amount
Purified water	balance

[0077]

Formulation Example 11: Face wash	wt%
L-1-Nal-Arg-LeuNH$_2$	0.5
Triethanolamine N-lauroylglutamate	25.0
Triethanolamine laurate	5.0
Poly(oxyethylene)(4)poly(oxypropylene)(11)butyl ether	5.0
Ethanol	3.0
Perfume	proper amount
Preservative	proper amount
Purified water	balance

[0078]

[Effects of the Invention]

The peptide derivatives of the present invention can inhibit the action of melanocyte-stimulating hormone, whereby pigmentation can be prevented, can prevent, improve or recover from immune abnormality or immunodeficiency, or regulate body weight by appetite control, and also can be used as cosmetics or external preparations for the skin, and in addition, can be

produced easily, and are excellent in the stability during storage.

JP1999-118633

[Document Name] ABSTRACT

[Abstract]

[Problems to be Solved by the Invention] To provide a melanocyte-stimulating hormone inhibitory agent which can prevent pigmentation, or can prevent, improve or recover from immune abnormality or immunodeficiency, or regulate body weight by appetite control, and also can be used as cosmetics or external preparations for the skin, and in addition, can be produced easily, and are excellent in the stability during storage.

[Means for Solving the Problems] A melanocyte-stimulating hornone inhibitory composition which comprises, as the active ingredient, at least one member selected from the group consisting of di- or tripeptides having a naphthyl group and their derivatives or the salts thereof.

[Selected Figure] None.